

## **The association between Alopecia areata and thyroid autoimmunity in Chinese adult patients: a controlled study.**

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### **Abstract**

**Background/Objectives:** Alopecia areata (AA) is a T cell-mediated autoimmune disease in association with other autoimmune diseases. This study aimed to investigate clinical significance of thyroid dysfunction and thyroid autoantibodies in Chinese adult patients with AA.

**Methods:** A questionnaire was used to collect data on demographic information, medical history, and family history of AA. Venous blood samples were obtained from 158 AA patients and 158 age- and gender-matched normal controls. Chemiluminescence was applied to measure serum levels of Thyroglobulin Antibody (TgAb), Thyroid Peroxidase Antibody (TPOAb), Free Triiodothyronine (FT3), Free Tetraiodothyronine (FT4) and Thyroid Stimulating Hormone (TSH).

**Results:** The positive frequency of TPOAb was significantly higher in AA patients than in control. Meanwhile, the positive frequency of TPOAb in the female patients with AA was 29.73%, significantly higher than that in the female controls. 22 of 158 AA patients (13.92%) were complicated with autoimmune thyroid diseases. Although we found no significant association between the frequency of thyroid autoantibodies and severity and duration of disease or family history of AA patients, positive frequencies of TgAb and TPOAb in the patients with more than one attack of AA were significantly higher than in the patients with only one attack of AA. There were no significant increases in FT3 and FT4 or TSH in AA patients compared to controls.

**Conclusions:** The incidence of autoimmune thyroid disease and positive frequency of TPOAb increase in Chinese AA patients. It is important to evaluate thyroid function and screen for thyroid autoantibodies in AA patients, especially in women of fertile age.

**Keywords:** Alopecia areata, Thyroid gland, Thyroiditis, Hypothyroidism, Chinese.

*Accepted on December 29, 2016*

### **Introduction**

Alopecia areata (AA) is a non-scarring hair disorder present in 1% of the general population [1]. Although environmental factors increase the incidence of susceptible individuals, the pathogenesis of AA is still not fully understood. It is considered that AA is an organ-specific, T cell-mediated autoimmune disease that targets anagen-stage hair follicles [2]. AA can be found in association with other autoimmune diseases and thyroid autoimmunity is probably the main disease associated with AA [3].

Currently, there is a lack of agreement on the overall prevalence of thyroid disease and thyroid function abnormalities in AA although the prevalence of thyroid disease in AA patients was reported to vary from 8% to 28% [4]. Surprisingly, the incidence of thyroid diseases in Chinese adult AA patients was reported to be low from 1.98% to 7.06% [5-7]. However, all of these studies are not case-control studies, so the prevalence of thyroid disease in Chinese adult AA patients may be not accurate compared to the studies in

other countries. Therefore, we performed this case-control study to better investigate the frequency of anti-thyroid autoantibodies and thyroid dysfunction in Chinese adult AA patients.

### **Subjects and Methods**

#### ***Study participants and data collection***

158 adult Chinese patients ( $\geq 18$  year old) diagnosed as AA in clinic of dermatology of Jinshan Hospital affiliated to Fudan University from year 2014 to 2015 were enrolled in this study. In all cases, a diagnosis of AA was made based on clinical examination by a group of experienced dermatologists. All the cases were excluded with the history of any thyroid diseases and other autoimmune diseases. The extent of AA at the time of first consultation was evaluated in accordance with the guidelines of the National Alopecia Areata Foundation guidelines [8]: S<sub>0</sub>: no hair loss; S<sub>1</sub>: <25% hair loss; S<sub>2</sub>: 26%-50% hair loss; S<sub>3</sub>: 51%-75% hair loss; S<sub>4</sub>: 76%-99% hair

loss; S<sub>5</sub>: total scalp hair loss, Alopecia totalis (AT); S<sub>5</sub>B<sub>2</sub>: total scalp and body hair, Alopecia universalis (AU). Mild AA was defined as S<sub>0</sub>, S<sub>1</sub>, or S<sub>2</sub>, and severe AA was defined as S<sub>3</sub>, S<sub>4</sub>, S<sub>5</sub>, or S<sub>5</sub>B<sub>2</sub>. All medical records were reviewed retrospectively and the data were collected retrospectively and systematically in a pre-established questionnaire. 158 healthy individuals whose age and gender matched with AA patients were enrolled as healthy control subjects, who had no family history of AA and other autoimmune diseases. An informed consent was taken from all participants, and the protocol was approved by Ethics Committee of the Jinshan Hospital of Fudan University.

### **FT3, FT4, TSH, TgAb and TPOAb assay**

Serum anti-thyroid autoantibodies (TgAb and TPOAb) and FT3, FT4 and TSH were assayed by chemiluminescence (Bayer AG, Leverkusen, Germany). The cutoff values of positivity for TgAb and TPOAb were 115 and 34 IU/ml, respectively. The normal range for FT3, FT4, and TSH were 3.1-6.8 pmol/L, 12-22 pmol/L, 0.27-4.2 pmol/L, respectively. Thyroid ultrasonography together with physical examination was performed to check thyroid volume which could be divided into I, II and III degree swelling. The diagnosis of autoimmune thyroid disease was performed as described previously [9].

### **Statistical analysis**

Data were analysed using SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). Student's t-test, chi-squared and Fisher's exact test were used for statistical analysis. Values

were given as mean ± SD, and P<0.05 was considered significant.

## **Results**

### **Demographics and clinical profiles**

158 Chinese adult patients were enrolled in this study, with a median age at 40 years (range 18-65 years old) and with duration of disease between one day and 2 years. Among them, 74 were females (46.84%) and 84 were males (53.16%), 80 (50.63%) were 18 to 40 years old, 74 (46.84%) were 41 to 60 years old, 4 (2.53%) were older than 60 years. 126 patients (79.75%) experienced their first attack of AA, 32 (20.25%) experienced more than one attack. 136 patients had mild AA and the other 22 patients had severe AA.

### **Thyroid parameters alteration in AA patients and healthy controls**

As shown in Table 1, the occurrence of thyroid parameters alteration was higher in AA patients than in control subjects ( $P=0$ ). 14 AA patients had thyroid dysfunction. The occurrence of thyroid autoantibodies was higher in AA patients than in control subjects ( $P=0.003$ ), among which the positive frequency of TPOAb was significantly higher than in control subjects ( $P=0.003$ ) while the positive frequency of TgAb was not significantly higher than in control subjects. There were no significant increases in the abnormal rates of FT3, FT4 and TSH in AA patients compared to controls.

**Table 1.** Comparison of altered thyroid parameters between AA and control groups.

Group	Case	Abnormality of Thyroid parameters	Positive autoantibodies	thyroid Positive	Positive TPOAb	Positive FT3	Positive FT4	Positive TSH
AA	158	54	44 (27.85%)	22(13.92%)	38 (24.05%)	12 (7.59%)	14 (8.86%)	11 (6.96%)
Control	158	25	22 (12.02%)	14	17 (10.76%)	4 (2.53%)	5 (3.16%)	8 (5.06%)
P-value		0	0.003	0.215	0.003	0.069	0.056	0.637

### **TgAb and TPOAb distribution in AA patients and healthy controls**

According to the age, AA patients and healthy controls were divided into three subgroups (18-40 years, 41-60 years and >60 years). There was no significant difference in the positive frequency of TgAb in AA patients at each age subgroup compared to controls. The positive frequency of TPOAb was more than 20% in AA group from 18 to 60 years old. Further analysis showed that among AA patients, the positive frequency of TPOAb in 18-40 years age subgroup was significantly higher than other age subgroups ( $P=0.014$ ), while there was no significant difference in the positive frequency of TPOAb at other age subgroups compared to controls. In addition, the positive frequency of TPOAb in female AA patients was significantly higher than female healthy controls ( $P=0.009$ ), while there was no significant difference in the

frequency of TPOAb or TgAb among male AA patients compared to controls (Table 2).

### **The correlation of TPOAb and TgAb positivity with the frequency of attack, disease duration, severity and family history of AA**

Statistical analysis showed that the positive frequencies of TgAb and TPOAb were significantly higher in AA patients with more than one attack than in those with only one attack, but they were not associated with disease duration, severity and family history of AA (Table 3).

### **Clinical diagnosis**

54 AA patients with abnormal thyroid function and thyroid auto-antibodies were followed-up every 3 months for 1 year.

Among them, 22 cases (13.92%) were diagnosed with autoimmune thyroid disease. Among 44 AA patients with positive TgAb and TPOAb, 15 cases (34.09%) (11 females and

4 males) was diagnosed with autoimmune thyroid disease later (7 AA patients with Hashimoto's thyroiditis, 5 Graves' disease, 3 primary hypothyroidism).

**Table 2.** TgAb and TPOAb distribution of the AA patients and control groups.

Group	18-40 years old	41-60 years old	>60 years old	Male	Female
<b>ATG</b>					
AA	10/80 (12.5%)	12/74 (16.22%)	0/4	4/84 (4.76%)	18/74 (24.32%)
Control	6/80 (7.5%)	8/78 (10.20%)	0	5/82 (6.10%)	9/76 (11.8%)
P value	0.43	0.34	>0.05	0.745	0.139
<b>TPO</b>					
AA	18/80 (22.5%)	20/74 (27.03%)	0/4	16/84 (19.05%)	22/74 (29.73%)
Control	6/80 (7.5%)	11/78 (14.10%)	0	8/82 (9.76%)	9/76 (11.84%)
P-value	0.014	0.069	>0.05	0.122	0.009

**Table 3.** The correlation of TPOAb and TgAb positivity with the frequency of attack, disease duration, severity and family history of AA.

Parameters	Positive TgAb	P value	Positive TPOAb	P value
Frequency of attack of AA		0.012		0.026
1	12/122 (9.84%)		24/122 (19.67%)	
>1	10/36 (27.78%)		14/36 (38.89%)	
The duration of the disease		0.748		0.299
≤ 1 year	18/134 (13.42%)		30/134 (22.39%)	
>1 year	4/24 (16.67%)		8/24 (33.33%)	
Severity of AA		0.514		0.788
Mild	18/136 (13.24%)		32/136	
Severe	4/22 (18.08%)		6/22 (27.27%)	
Family history of AA		0.359		1
Positive	0/10		2/10 (20%)	
Negative	22/148 (14.86%)		36/148 (24.32%)	

## Discussion

AA is an ancient disease known to Egyptians even before Christ [4]. Despite its long history, the pathogenesis of AA remains elusive. Up to now, it is considered that AA is an autoimmune disease often associated with other autoimmune diseases. Thyroid diseases were observed to be the most common comorbid disorder in AA patients, including hypothyroidism, Hashimoto's thyroiditis, Graves' disease and simple goitre [10]. Previous studies showed that the incidence of thyroid disease has varied from 8% to 28% in AA patients [4]. In China, the incidence of thyroid disease in AA patients was rarely reported and the only available data were based on

non-controlled studies [5-7]. The aim of this controlled study was to determine whether the incidence of thyroid autoimmunity or thyroid function abnormalities in Chinese AA patients is similar to that reported in other countries.

First we detected the concentrations of FT3, FT4 and TSH to evaluate thyroid function of AA patients and normal controls. We found no significant differences in the concentrations of FT3, FT4 and TSH between AA patients and normal controls, suggesting that there was no obvious damage on thyroid function in AA patients. Many skin disorders such as AA can be seen in patients with autoimmune thyroid disease, independently of thyroid function. Most of the time, there is no cause-effect relationship but the association is probably part of the same immune dysfunction [11].

However, 54 of 158 cases (34.18%) of AA had abnormalities of thyroid hormone and thyroid autoantibodies, significantly higher than normal controls (16%). In subsequent clinical diagnosis, 22 of 158 cases (13.92%) were diagnosed with autoimmune thyroid disease; the incidence was higher than the results reported in Beijing (6.7%) [7] and in Singapore (2.3%) [12], was lower than that reported in Spain (22%) [13] and in India (18.3%) [14], but was similar to that in American (14.6%) [15]. Hashimoto's thyroiditis accounted for the majority of autoimmune thyroid disease in this study, while primary hypothyroidism was the main disease reported in previous studies. This is reasonable because Hashimoto's thyroiditis is the main reason of primary hypothyroidism [16]. There are clinical and biochemical overlaps between Hashimoto's thyroiditis and hypothyroidism, and it is not surprising that the same dermatologic manifestations occur in both diseases.

Thyroid autoantibodies are secondary immune response markers of thyroid damage. The abnormality rate of thyroid autoantibodies in AA group was 27.85% in our study, significantly higher than that in control group (12%, P<0.05). Our results are consistent with the results of previous clinical

studies [4,17]. We found that the frequency of TPOAb abnormality was 24.05%, similar with the results in Beijing [7] but lower than that in India (48%) [10]. It may be due to less sample (only 50 AA patients) enrolled in that study [10], which could lead to statistics bias.

Thyroid Peroxidase (TPO) is a key enzyme in the formation of thyroid hormones and a major autoantigen in autoimmune thyroid diseases. Titers of TPOAb are correlated with the degree of lymphocytic infiltration in euthyroid subjects. It has been suggested that the frequency of TPOAb may serve as a marker of future thyroid failure [17]. Roos et al. found that the incidence of hypothyroidism during 9 years of follow-up was significantly higher in subjects with positive TPOAb compared to TPOAb negative subjects, even if the thyroid function was in the normal range [18]. Prummel et al. suggested that measuring TPOAb in euthyroid subjects could be used to identify subjects with increased risk of hypothyroidism [19]. Thus follow-up in euthyroid subjects with AA and positive TPOAb is very important, even if these patients do not need any treatment temporarily.

In addition, our study showed that the positive frequency of TPOAb in female patients was slightly more than that in male patients. Moreover, the positive frequency of TPOAb in female patients 18 to 40 years old was significantly higher than that of the corresponding age subgroup in control group. In women of fertile age, TPOAb is associated with increased abortion rate and obstetric problems. In particular, TPOAb positive women are prone to develop hypothyroxinemia during pregnancy and thyroid dysfunction after delivery. About 50% of TPOAb positive pregnant women develop postpartum thyroiditis, and among them more than 40% are affected by permanent hypothyroidism that develops in subsequent years [20]. Therefore, our results support the recommendation for annual assessment of thyroid function parameters including TPOAb in all patients with AA [7,10,13,21].

There is a lack of agreement on the relationship between thyroid autoantibodies and severity and family history of AA. Yang et al. found that compared with the patients without TPOAb, those with TPOAb showed a significant increase in the proportion of AA patients with early onset (<18 years), prevalence rate of AT/AU and thyroid diseases, and incidence rate of AA in first degree relatives [7]. However, earlier report suggested that the frequency of thyroid autoantibodies has no clinical correlation with AA severity [22]. Serarslan et al. also did not find the correlation between AA disease severity and personal and family history of autoimmune disease [23]. Kasumagic et al. compared the frequency of thyroid autoantibodies (TgAb, TPOAb) in 70 AA patients and 30 healthy volunteers. Thyroid functional abnormalities were found in 8 (11.4%) AA patients and positive autoimmune antibodies were associated with AA in 18 (25.7%) patients, with no significant association between the disease severity and presence of these antibodies [21]. In our study, there was no significant association between the frequency of thyroid autoantibodies and severity and duration of disease or family history of the patient with AA. However, we found higher

positive rate of TgAb and TPOAb in the patients with more than one attack of AA than in the patients with only one attack of AA. Previous studies have shown that AA is associated with various psychiatric comorbidities [24]. In this study we did not examine the psychiatric comorbidities of AA patients, which warrant further studies.

In summary, we demonstrated that the incidence of autoimmune thyroid disease and positive rate of TPOAb increased in Chinese adult AA patients compared to healthy controls. Our results are consistent with previous studies and suggest that it is important to evaluate thyroid function and screen for thyroid autoantibodies in AA patients even without clinical manifestations of thyroid diseases, especially in women of fertile age.

### Conflict of Interest

The authors declare no conflict of interest.

### Acknowledgement

This work was supported by the science and technology committee of Jinshan District in Shanghai, China (No. 2013-3-12).

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